DETAILED ACTION

In view of the appeal brief filed on 19 October 2009, PROSECUTION IS HEREBY REOPENED. See the rejections set forth below.

To avoid abandonment of the application, appellant must exercise one of the following two options:

(1) file a reply under 37 CFR 1.111 (if this Office action is non-final) or a reply under 37 CFR 1.113 (if this Office action is final); or,

(2) initiate a new appeal by filing a notice of appeal under 37 CFR 41.31 followed by an appeal brief under 37 CFR 41.37. The previously paid notice of appeal fee and appeal brief fee can be applied to the new appeal. If, however, the appeal fees set forth in 37 CFR 41.20 have been increased since they were previously paid, then appellant must pay the difference between the increased fees and the amount previously paid.

A Supervisory Patent Examiner (SPE) has approved of reopening prosecution by signing below.

Claims 1-20 and 24-31 have been cancelled.

Claims 21-23 and 32-34 are pending and currently examined.

WITHDRAWN REJECTION

The rejection of claims 21-23 and 32-34 under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement is withdrawn in favor of the following new grounds of rejection.

NEW REJECTIONS

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 21-23 and 32-34 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for *in vitro* preventing and inhibiting lymphocyte activation by contacting lymphocyte cells with isolated Vpr protein, does not reasonably provide enablement for a method for *in vivo* preventing and inhibiting lymphocyte activation by contacting lymphocyte cells with isolated Vpr protein. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

In making a determination as to whether an application has met the requirements for enablement under 35 U.S.C. 112, first paragraph, the courts have put forth a series of factors (MPEP §2164.01(a)). See, *In re Wands*, 8 USPQ2d 1400, at 1404 (CAFC 1988); and Ex Parte Forman, 230 U.S.P.Q. 546 (BPAI 1986). The factors that may be considered include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. Id. While it is not essential that every factor be examined in detail, those factors deemed most relevant should be considered.

The nature of the invention is the inhibition and prevention of lymphocyte activation by Vpr protein. The breadth of the claims encompasses both HIV-infected and non-HIV-infected B lymphocytes and T lymphocytes and both *in vitro* and *in vivo* prevention and inhibition.

The disclosure fails to provide any working embodiments that meet the claimed limitations. While there are examples of assays to identify Rip-I-binding fragments of Vpr that are inducers or inhibitors of glucocorticoid receptor (GR) type II complex translocation from cytoplasm to the nucleus (page 45-54), no *in vitro* or *in vivo* working example of any prevention or inhibition of lymphocyte activation is disclosed in the specification.

The specification provides limited *in vitro* guidance regarding practice of the claimed methods. The specification refers generally to the Vpr's interaction with the glucocorticoid steroid biochemical pathway (page 22, line 26-37), that the expression of Vpr within the cell causes the cell to stop proliferating (page 5, line 31-35) and that Vpr inhibits cytokine production/secretion by T cells, B cells, and monocytes during immunoglobulin activation (page 10, lines 14-20). However, the disclosure is silent pertaining to specific method steps of inhibition and prevention of lymphocyte activation *in vivo*.

The disclosure fails to provide any guidance pertaining to the structural characteristics or mechanisms of the interaction between Vpr and lymphocytes. The specification specifically discloses in more details and in working examples the use of the Vpr protein or the Rip-I- binding fragments of Vpr protein as transfection agent for

the delivery of conjugated nucleic acid molecule or derivatives into the nucleus of a cell (page 36-37), which is not remotely related to inhibition or prevention of lymphocyte activation. Therefore, the disclosure does not correlate with the claimed method of preventing and inhibiting lymphocyte activation *in vitro* or *in vivo*, especially inside humans, with respect to how to target B or T lymphocytes *in vivo* or what is the effective amount to prevent activation or to inhibit cytokine production and secretion by immunoglobulin activation.

At the time the invention was made, successful implementation of lymphocyte activation inhibition and prevention with Vpr was not routinely practiced by those skilled in the art. Prior art only teaches T lymphocytes to secrete cytokines upon activation (Mosmann, 1997) and B lymphocytes to produce immunoglobulins once activated by cytokines (Paul, 1987). The only effect of Vpr expression within cells is the alteration of distribution of cells in the cell cycle and thereby mediating the prevention of cell proliferation (Rogel, February 1995). The prior art is unpredictable and fails to provide sufficient illumination pertaining to the mechanisms underlying inhibition and prevention of lymphocyte activation by the Vpr protein *in vivo*. Planelles *et al.* reported that Vpr protein induces cell growth inhibition and/or death while facilitating HIV-1 viral replication with in an infected proliferating population of peripheral blood lymphocytes (Planelles, September 1995). More importantly, Levy *et al.* (Levy, 1994) discovered that humoral immunity modulates Vpr activity in vivo because anti-Vpr antibodies inhibited serum Vpr activity. Therefore, once in the presence of anti-Vpr antibodies, contacting

lymphocyte cells with an isolated Vpr protein *in vivo* does not prevent or inhibit lymphocyte activation.

There is no specific guidance in the prior art and no specific examples of the claimed *in vivo* method set forth in the specification. While Applicant is not required to set forth working examples, the specification must set forth sufficient teachings to allow one to practice the claimed invention. Legal precedence dictates that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification. *In re Fisher*, 427 F.2d 833, 839, 166 U.S.P.Q. 18 24 (C.C.P.A. 1970). *In re Vaeck*, 20 U.S.P.Q.2d 1438 (C.A.F.C 1991). *In re Angstadt*, 537 F.2d 498, 502-03, 190 U.S.P.Q. 214, 21 (C.C.P.A. 1976). There is no evidence that Vpr has the preventative and inhibitibe effect on the activation of T lymphocytes or B lymphocytes *in vivo*. Thus, when all the aforementioned factors are considered in *toto*, it would clearly require undue and unpredictable experimentation from the skilled artisan to practice the claimed invention.

In conclusion, the instant invention, based on the evidence as a whole, in light of the factors articulated by the court in *In re Wands*, lacks an enabling disclosure.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. §103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 21-23 and 32-34 are rejected under 35 U.S.C. §103(a) as being unpatentable over Rogel *et al.* (February 1995, cited in IDS, hereinafter "Rogel") in view of Macreadie *et al.* (March, 1995, hereinafter "Macreadie").

Claims 21 and 32 are directed to a method comprising contacting lymphocyte cells with isolated HIV Viral Protein R (Vpr). Claim 21 additionally recites the intended use of preventing lymphocyte activation whereas claim 32 additionally recites the intended use of inhibiting lymphocyte activation. Claims 22 and 33 further limit the lymphocyte cells to T cells. Claims 23 and 34 further limit the lymphocyte cells to B cells.

Rogel discloses transfection with plasmids that express Vpr alone and indicate that Vpr expression can arrest cell cycle at the G2 phase (page 886, under the title "Expression of Vpr alone alters the distribution of cells in the cell cycle") and therefore may mediate its effect through prevention of cell proliferation (page 882, right column, lines 14-17; and page 887, Discussion, last two paragraphs).

Rogel does not disclose obtaining an isolated Vpr protein.

Macreadie discloses contacting yeast cells with an isolated Vpr protein in the method step of electroporation (page 2771, left column, last paragraph), which causes cell growth arrest (page 2771, right column).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the Rogel method by replacing the plasmid with isolated Vpr protein peptide as suggested by Macreadie with a reasonable expectation of success because the prior art suggests that both the Vpr-expressing plasmid and the

isolated Vpr protein can cause cell cycle arrest. One having ordinary skill in the art would have been motivated to make such a modification to more directly affect the lymphocyte proliferation. There would have been a reasonable expectation of success, given the simple substitution of one known method step of inhibition and preventing cell proliferation, by a plasmid expressing Vpr protein inside the cells, for another functional equivalence, by the isolated Vpr protein itself as known in the prior art, would obtain predictable results of the same functional purpose of arresting cell growth and thereby inhibiting and prevention lymphocyte cell proliferation. See MPEP 2144.06 [R-6] Art Recognized Equivalence for the same purpose >II. < SUBSTITUTING EQUIVALENTS KNOWN FOR THE SAME PURPOSE. Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

The limitation of "preventing or inhibiting lymphocyte activation" is inherently obvious over the combined teachings of the Rogel and Macreadie since the prior art references together disclose the same method step as claimed. MPEP §2112 [R-3] states: The express, implicit, and inherent disclosures of a prior art reference may be relied upon in the rejection of claims under 35 U.S.C. 102 or 103. "The inherent teaching of a prior art reference, a question of fact, arises both in the context of anticipation and obviousness." *In re Napier*, 55 F.3d 610, 613, 34 USPQ2d 1782, 1784 (Fed. Cir. 1995) (affirmed a 35 U.S.C. 103 rejection based in part on inherent disclosure in one of the references). Newly discovered property of prior art cannot support patent on that same art. *Abbott Laboratories v. Baxter Pharmaceutical Products Inc.* 80

USPQ2d 1860, U.S. Court of Appeals Federal Circuit Nos. 06-1021, -1022, -1034. Thus the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. *In re Best*, 562 F.2d 1251, 1254, 195 USPQ 430, 433 (CCPA 1977). See also MPEP §2141.02 [R-5] V. *In re Papesch*, 315 F.2d 381, 391, 137 USPQ 43, 51 (CCPA 1963) ("From the standpoint of patent law, a compound and all its properties are inseparable."). Obviousness cannot be predicated on what is not known at the time an invention is made, even if the inherency of a certain feature is later established. *In re Rijckaert*, 9 F.2d 1531, 28 USPQ2d 1955 (Fed. Cir. 1993). Absent evidence to the contrary, the limitation of "preventing or inhibiting lymphocyte activation" is inherently obvious over the method step of contacting lymphocyte cells with an isolated Vpr proteins as disclosed by Rogel in view of Macreadie.

Conclusion

No claim is allowable.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louise Humphrey whose telephone number is 571-272-5543. The examiner can normally be reached on Mon-Fri, 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert Mondesi, can be reached on 571-272-0956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/L. H./
Examiner, Art Unit 1648
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